REMARKS/ARGUMENTS

Favorable reconsideration of this application, as presently amended and in light of the following discussion, is respectfully requested.

Claims 28-31 and 35-43 are presently pending in this application, Claims 32-34 having been canceled, Claims 28-31 and 38 having been amended, and Claims 39-43 having been newly added by the present amendment. Support for the amendments and addition in the claims can be found in the original application, for example, the specification, paragraphs 0032-0034. Thus, no new matter is believed to be added. If, however, the Examiner disagrees, the Examiner is invited to telephone the undersigned who will be happy to work in a joint effort to derive mutually satisfactory claim language.

In the Final Office Action of November 26, 2010, Claim 16 was rejected under 35 U.S.C. §102(e) as being anticipated by Bisgaier et al. (U.S. Publication 2004/0038891); and Claims 16 and 18-38 were rejected under 35 U.S.C. §103(a) as being unpatentable over Bisgaier et al. as evidenced by Welch et al. (U.S. Publication 2006/0257866).

Claim 28 is directed to a method for improving prognosis, neurological symptoms, or motor dysfunction of a disease resulting from cerebral infarction. As currently amended, Claim 28 recites "intravenously administering an effective amount of paraoxonase to improve one of prognosis, neurological symptoms and motor dysfunction of a disease resulting from cerebral infarction to a patient in need thereof."

The Office Action states that "Bisgaier teaches that the method is useful in any context where treatment from ischemic reperfusion is useful to include the brain, or is cerebral in nature (0016)." The rejection is apparently based on several statements in Bisgaier et al. Specifically, Bisgaier et al. states that it provides methods "for treating, reducing or preventing ischemic reperfusion injury using compositions comprising apolipoproteins, lecithin cholesterol acyltransferase or paroxonase," and that "[t]he methods

and compositions of the invention can be useful in any context where treatment, reduction or protection from ischemic reperfusion injury might be useful" (paragraph 0016). The reference also states that "[i]n certain embodiments, the methods and compositions of the invention can protect the muscle and organs such as, for example, the heart, liver, kidney, brain, lung, spleen and steroidogenic organs ... from damage as a result of ischemia reperfusion injury" (paragraph 0016).

Applicants respectfully submit that amended Claim 28 is not obvious from Bisgaier et al. and Welch et al. because the references fail to provide reasonable expectation of success of intravenous administration of an effective amount of paraoxonase to improve one of prognosis, neurological symptoms and motor dysfunction of a disease resulting from cerebral infarction to a patient in need thereof.

As stated in MPEP 2143.02, an obviousness rejection requires showing of a reasonable expectation of success determined at the time the invention was made. *See Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1207-08, 18 USPQ2d 1016, 1022-23 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success.). According to MPEP 2143, "[t]he rationale to support a conclusion that the claim would have been obvious is that 'a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.'"

Here, Bisgaier et al. and Welch et al. fail to provide bases to conclude that a person of ordinary skill had good reason to pursue "intravenously administering paraoxonase to improve one of prognosis, neurological symptoms and motor dysfunction of a disease resulting from cerebral infarction" as recited in amended Claim 28.

In order for a substance to be effective against diseases resulting from cerebral infarction, the substance needs to be effectively distributed in the brain without blockage by

the blood-brain barrier. Paraoxonase (PON), apolipoprotein (APO), lecithin cholesterol acyltransferase (LCAT) are proteins, and Bisgaier et al. discloses nothing that leads to the expectation that protein substance such as PON can successfully pass through the blood-brain barrier to be satisfactorily distributed in the brain. In fact, the reference presents no experimental results of PON which suggest any therapeutic effect against diseases resulting from cerebral infarction.

Regarding substances other than PON, Bisgaier et al. provides descriptions regarding LCAT and ECT-216. However, nothing in Bisgaier et al. suggests that PON and other substances (LCAT and ECT-216) are expected to have common pharmacological action in treatment of a disorder resulting from ischemia reperfusion or cerebral infarction. For example, Bisgaier et al. simply describes LCAT as "the enzyme that catalyzes the transacyation of lecithin" (paragraph 0047), and does not show that LCAT has pharmacological function to suppress action against lipid peroxidation. Also, Bisgaier et al. presents experimental results regarding ECT-216, but ECT-216 is a complex of ApoA-I and a phospholipid, and the experimental results provided in Bisgaier et al. only relate to effectiveness in heart protection. In addition, Bisgaier et al. only discusses the study on the heart protection effect of ECT-216 based on experimental animals, and the experimental results provided in Bisgaier et al. do not demonstrate effectiveness of APO itself. Specifically, Examples 1 to 4 use vehicles as control (2% glucose solution in Example 1; see Fig. 12), and Examples 2 to 4 employ a sucrose-mannitol solution as control (see Figs. 15 and 18). The phospholipid as the component of ECT-216 is not contained in the vehicles as control, and therefore the effect of the phospholipid as the component of ECT-216 cannot be disregarded in the evaluation of effectiveness of APO against the disorder resulting from ischemia reperfusion. Accordingly, Bisgaier et al. does not show effectiveness of APO itself (not in the form of the complex with the phospholipid) for preventive and therapeutic

treatments of disorders resulting from ischemia reperfusion or diseases resulting from cerebral infarction.

Even if the experimental results in Bisgaier et al. have any significance regarding the effectiveness of apolipoprotein itself, PON is distinct from apolipoproteins, and thus one cannot reasonably expect to have the same effectiveness as apolipoproteins. In this regard, Applicants wish to bring the Examiner's attention to the literatures attached herewith as Appendix A and Appendix B. Appendix A is Warden et al. (Atherosclerosis in Transgenic Mice Overexpressing Apolipoprotein A-II, Abstract of Science, 261, pp. 469-471, 1993), and Appendix B is Metlum et al. (Overexpression of human lecithin: cholesterol acyltransferase in mice offers no protection against diet-induced atherosclerosis, Abstract of APMIS, 108, pp. 336-342, 2000).

Warden et al. reports experimental results obtained by using transgenic animals overexpressing either ApoA-I or ApoA-II. Both ApoA-I and ApoA-II are fundamental components of high density lipoproteins (HDL). According to Warden et al., ApoA-I may have antiatherogenic function, but ApoA-II has proatherogenic function. Also, according to Metlum et al., LCAT has no protecting action on diet-induced atherosclerosis. These reports indicate that, although ApoA-I and ApoA-II are both categorized in the same class (HDLs), ApoA-I and ApoA-II cannot be expected to have the same preventive and therapeutic effectiveness. Thus, even assuming, *arguendo*, that experimental results in Bisgaier et al. suggest certain therapeutic effect of apolipoprotein itself, they do not provide any expectation about therapeutic effect of PON which is distinct from APO.

For the foregoing reasons, Applicants respectfully submit that Bisgaier et al. does not provide reasonable expectation of success of intravenous administration of PON against diseases resulting from cerebral infarction.

Welch et al. refers to CHAPS as an example of surface active agents that might reduce non-specific binding of the target RNA (see paragraph 0138). Welch et al. also refers to CHAPS as an additive for preparation of colloidal suspension of beads (see paragraph 0193). However, the reference fails to teach or suggest the intravenously administration of paraoxonase as recited in Claim 28. Also, nothing in the reference provides reasonable expectation of success of the intravenously administration of paraoxonase against diseases resulting from cerebral infarction. For example, Welch et al. does not discuss effectiveness of CHAPS on a disorder resulting from cerebral infarction when CHAPS is administered in vivo together with APO, PON or LCAT. Therefore, Welch et al. cannot cure the deficiencies of Bisgaier et al.

For the foregoing reasons, Claim 28 is believed to be allowable. Furthermore, since Claims 29-31 and 35-38 depend from Claim 28, substantially the same arguments set forth above also apply to these dependent claims. Hence, Claims 29-31 and 35-38 are believed to be allowable as well.

In view of the amendments and discussions presented above, Applicants respectfully submit that the present application is in condition for allowance, and an early action favorable to that effect is earnestly solicited.

Respectfully submitted,

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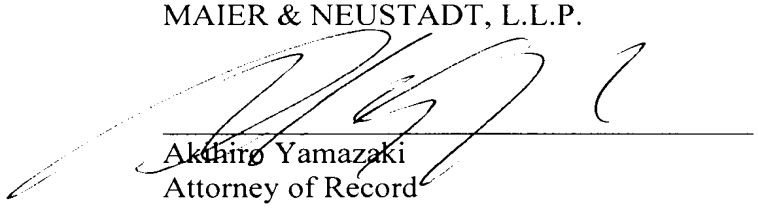

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